Natural Product Synthesis

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Total Synthesis of Cyathin A_3 and Cyathin B_2**

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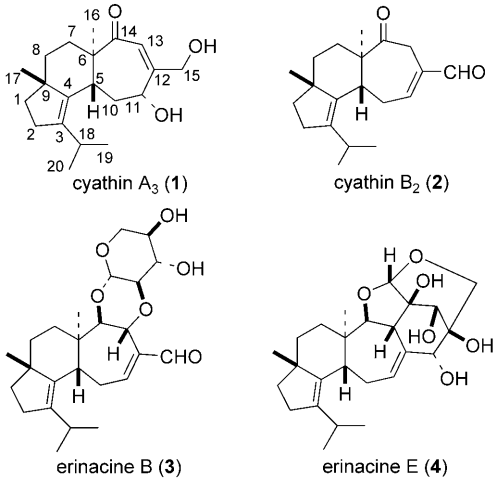
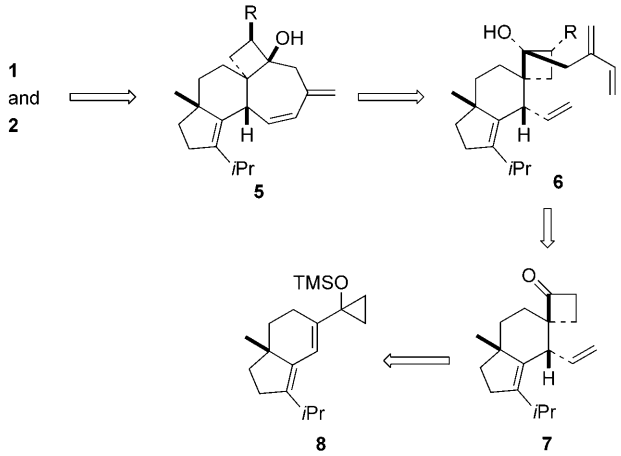
The cyathin diterpenes, which were isolated from bird's nest fungi by Ayer and co-workers, are known to display a wide range of interesting biological properties.[1,2] The isolation of many structurally related metabolites such as striatins, scabronines, sarcodonins, erinacines, and cyanthiwigins has been reported in recent years. A great majority of these cyathane metabolites possess a unique 5/6/7-tricyclic skeleton with a *trans* 6/7-ring junction, as exemplified by cyathin A_3 (**1**), cyathin B_2 (**2**), erinacine B (**3**), and erinacine E (**4**). Some



cyathins have been reported to stimulate nerve growth factor synthesis and might thus serve as a useful lead in identifying small molecules that have neurotrophic activity with potential application in combating neurodegenerative disorders.[3] The novel structure and significant bioactivity of these cyathane diterpenoids, coupled with their low natural abundance, spurred synthetic studies, and several elegant syntheses were recently disclosed.[4–9] Herein, we report a stereoselective synthesis of cyathin A_3 (**1**) and cyathin B_2 (**2**) by a Prins-type reaction of a cycloalkenyl cyclopropanol and subsequent elaboration of the resulting spirocyclobutanone ring.

Toward the development of a unified approach for the synthesis of cyathane diterpenoids, we selected **1** and **2** as our initial targets. The key challenges center around the surprisingly difficult diastereocontrol of the *trans* 6/7-ring junction relative to the methyl group at C9 and the juxtaposition of the remaining functionalities. As outlined in the retrosynthesis in Scheme 1, we envisioned the construction of a seven-membered core **5** by ring-closing metathesis (RCM) of **6** and subsequent elaboration of the resulting product **5**. Substrate **6** could be prepared from spirocyclobutanone **7**, which would be available by a Prins-type reaction of vinylcyclopropanol **8** with a suitable acetal. The use of a spirocyclobutanone ring as the key quaternary carbon scaffold could present an attractive solution to the requisite diastereocontrol, wherein formation of the two newly formed C–C bonds was anticipated to take place from the opposite side of the angular methyl group.



Scheme 1. Retrosynthetic analysis of cyathin A_3 (**1**) and cyathin B_2 (**2**). TMS = trimethylsilyl.

Our synthesis began with the known dienoate **9** (Scheme 2).[4b,10] The Kulinkovich cyclopropanation of **9** with EtMgBr, and subsequent silylation of **10** delivered **8**.[11] Treatment of **8** with acetal **11** in the presence of $TiCl_4$ afforded predominantly (>15:1) two isomers **12β,α** (78%) in a separable 10:3 ratio.[12a] The stereochemistry of the major isomer **12β** was firmly established by a single-crystal X-ray analysis.[12b] Reductive elimination of both **12β,α** with Zn dust cleanly gave **7** in 85% yield as the sole product, thus ascertaining the epimeric relationship at C10 between **12β** and **12α**. It was next necessary to introduce the second alkene moiety from the more hindered face of the cyclobutanone ring to set the stage for the pivotal RCM reaction.[13] Toward this end, an aldol reaction of cyclobutanone **7** with benzaldehyde was undertaken and provided **13a** in 81% yield, essentially as one isomer. The stereochemistry of the aldol product **13a** was assigned on the basis of the Zimmerman–Traxler transition state model. A suitably functionalized

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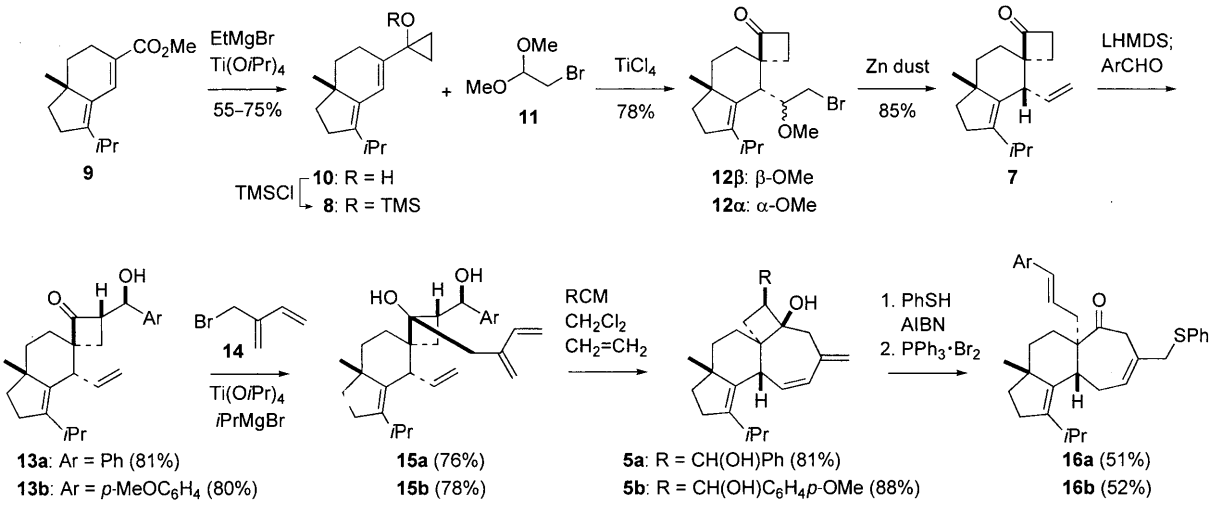
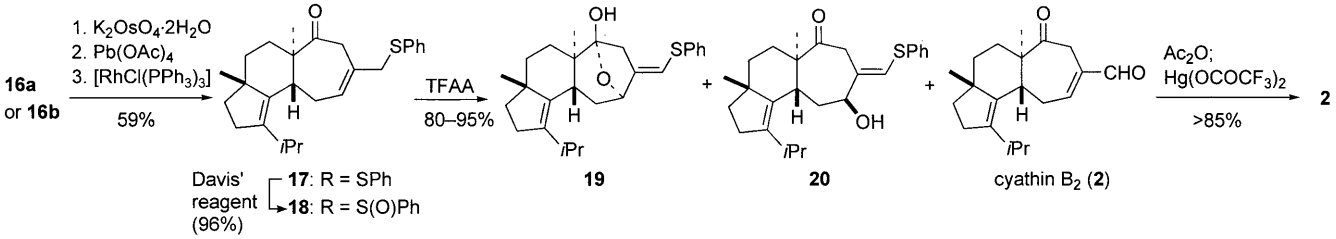


Scheme 2. Construction of the tricyclic core. AIBN = 2,2′-azobisisobutyronitrile, HMDS = 1,1,1,3,3,3-hexamethyldisilazane.

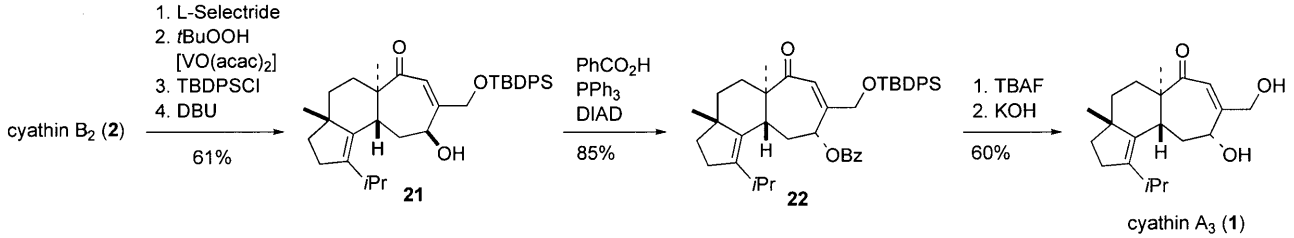
allylation reagent was generated from **14**.[14–16] Subsequent addition of **14** to cyclobutanone **13a** afforded the corresponding adduct **15a** in 76% yield. Ring-closing metathesis of **15a** by the second-generation Grubbs catalyst proceeded cleanly to furnish **5a** in 81% yield. Addition of thiophenol[17] to diene **5a** and subsequent Grob fragmentation of the cyclobutanone ring then provided **16a** in respectable yield.

With the tricyclic core **16a** now complete, the remaining tasks entailed cleavage of the styrene moiety and elaboration of the allylic sulfide functionality to complete a total synthesis of **1** and **2** (Scheme 3). Regioselective dihydroxylation of **16a** under Sharpless' asymmetric dihydroxylation conditions[18] proceeded very slowly to give the corresponding diol (67% based on recovered starting material). The *p*-methoxystyrene derivative **16b** was thus prepared to avoid cumbersome recycling of recovered **16a**. Osmylation of **16b** was indeed more facile and afforded the respective diol in 74% yield. Oxidative cleavage of these diols with lead(IV) acetate, and subsequent decarbonylation of the resulting aldehyde with the Wilkinson catalyst delivered **17**. The allylic sulfide functionality of **17** was then elaborated by means of a Pummerer rearrangement of sulfoxide **18**.[19,20] The latter was next prepared by use of Davis' oxaziridine[21] as a 1:1 diastereomeric mixture in 96% yield. Exposure of **18** to TFAA produced cyathin B_2 (**2**), along with vinyl sulfides **19** and **20**, in 80–95% combined yield.[22,23] Most conveniently, the crude mixture (10:3:7) of these products was subjected, without separation, to acetylation and subsequent hydrolysis by $Hg(OCOCF_3)_2$ to afford **2** in approximately 90% yield.

Cyathin B_2 (**2**) was then converted into cyathin A_3 (**1**) by standard methods (Scheme 4). Chemoselective reduction of **2** by L-selectride and subsequent epoxidation of the resulting



Scheme 3. Total synthesis of cyathin B_2 (**2**). TFAA = trifluoroacetic anhydride.



Scheme 4. Total synthesis of cyathin A_3 (**1**). acac = acetylacetonate, Bz = benzoyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIAD = diisopropylazodicarboxylate, TBAF = tetra-*n*-butylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl.

allylic alcohol gave the β-epoxide in greater then 10:1 selectivity. Protection of the primary alcohol and subsequent ring opening of the epoxide with DBU afforded **21** in 61% overall yield. The Mitsunobu inversion of **21** with benzoic acid proceeded cleanly to give **22** in 85% yield. Cyathin A_3 (**1**) was then secured by sequential removal of the two protecting groups and its bis-acetate was also prepared for additional characterization.[1,8,24]

In summary, cyathin A_3 (**1**) and cyathin B_2 (**2**) have been synthesized by utilizing a Prins-type reaction of a vinyl cyclopropanol as the stereocontrolling step and the resulting spirocyclobutanone ring is used in an efficient RCM reaction to stereoselectively construct a suitably functionalized seven-membered ring. Additional studies on erinacines and their congeners, as well as enantioselective syntheses of **1**–**4**, will be reported in due course.

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[20] The [2,3]-sigmatropic rearrangement of **18** in the presence of a thiophile (e.g., trimethylphosphite) gave a 3:1 mixture of two allylic alcohols in quantitative yield: the α-alcohol exists predominantly as the hemiacetal.

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[22] The geometry of the double bond of the vinyl sulfides was determined by NOE measurements.

[23] The configuration of the C11 alcohol was tentatively assigned by the known preference of cyathin A_3 for the hemiacetal form and was also confirmed by X-ray analysis (Dr. Mary Jane Heeg) of a related compound. CCDC 640599 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[24] Stereoselective reduction of **22** was achieved by L-Selectride to afford the corresponding β-alcohol at C14, the spectroscopic data of which were in excellent agreement with those of Nakada and co-workers.[9] Interestingly, this stereochemical outcome contrasts with the Nakada procedure under the control of the Corey–Bakshi–Shibata reagent.[25] Reduction of **2** with an excess of L-selectride gave small amounts of the corresponding β-diol at C14, along with large amounts of the primary alcohol (without ketone reduction; see Scheme 4). Reduction of **2** with diisobutylaluminum hydride gave a 1:3 mixture of the corresponding β- and α-diol, respectively.

[25] The enantiopure β-alcohol obtained from **22** was recently converted into (−)-**3** and (−)-**4** by Nakada and co-workers.[9] Albeit our alcohol product is racemic, this work can be viewed as a formal synthesis of **3** and **4**.

